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CKD-EPI equation: A suitable Glomerular Filtration Rate estimate for drug dosing in HIV-infected patients

Équation CKD-EPI : un estimateur du débit de filtration glomérulaire utile pour l'adaptation posologique chez les patients infectés par le VIH

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Abstract

Objectives. - To evaluate concordance between glomerular filtration rate (GFR) estimates (Cockcroft and Gault, modification of diet in renal diseases, chronic kidney disease epidemiology study group equations) for drug dosing in HIV-infected patients.
Patients and methods. - We performed a monocentric study. GFR was measured using the gold standard method (plasma clearance of iohexol) in 230 HIV-infected patients. Concordance rate was evaluated between measured GFR (mGFR) and estimated GFR (eGFR) for different GFR categories (GFR > 90 mL/min, GFR < 90 mL/min, GFR > 70 mL/min, and GFR < 70 mL/min). MDRD and CKD-EPI were used with and without indexation to body surface area (BSA).
Results. - Mean age was 48 ± 10 years, mean mGFR was 101 ±26 mL/min. Concordance between mGFR and eGFR estimated with CG, CKD-EPI (indexed and not indexed to BSA), or MDRD equations (not indexed to BSA) was similar (73%, 73%, 74%, and 73% respectively) for a breakpoint value of 90 mL/min for GFR. At this value, the concordance rate between mGFR and MDRD indexed to BSA was significantly lower (65%, $P < 0.05$). Using 70 mL/min of GFR as the breakpoint value, ail equations had similar concordance rates with mGFR (with or without indexation to BSA).
Conclusion. - CKD-EPI equation has the same concordance with GFR and with CG when used for drug dosing.

Résumé

Objectifs. - Évaluer la concordance entre l'estimation du débit de filtration glomérulaire (DFG) grâce aux équations de Cockcroft et Gault, MDRD, CKD-EPI et une méthode de mesure du DFG pour l'adaptation posologique des antirétroviraux chez les patients infectés par le VIH.
Patients et méthodes. - Étude monocentrique ; 230 patients suivis pour une infection à VIH. Estimation de la concordance entre DFG estimé et DFG mesuré à différentes catégories de DFG : > 90 mL/min, < 90 mL/min, > 70 mL/min et < 70 mL/min. Les équations MDRD et CKD-EPI ont été utilisées indexées et désindexées à la surface corporelle (SC).
Résultats. - L'âge moyen des patients était de 48 ± 10 ans, le DFG mesuré moyen était de 101 ± 26 mL/min. La concordance entre le DFG mesuré et le DFG estimé par la formule CG, la formule CKD-EPI (indexée ou non à la SC) ou la formule MDRD (non indexée à la SC) est similaire pour classer le DFG en dessous ou au-dessus de 90 mL/min (respectivement 73 %, 73 %, 74 %, 73 %). À cette valeur, la concordance entre DFG mesuré et MDRD indexé à la SC est significativement moins bonne à 65 % (p<0,05). Pour des valeurs de DFG ≥ ou < 70 mL/min, toutes les équations ont des taux de concordance avec le DFG mesuré similaires (avec ou sans l'indexation à la surface corporelle) de 86 à 90 %.
Conclusion. - L'équation CKD-EPI est aussi concordante avec une mesure du DFG qu'avec la formule CG pour l'adaptation posologique des antirétroviraux.

Keywords*:* HIV infection; Glomerular filtration rate; Cockcroft and Gault; CKD-EPI

Mots clés *:* Infection par le VIH ; Débit de filtration glomérulaire ; Cockcroft et Gault ; CKD-EPI

1. Introduction

Glomerular filtration rate (GFR) estimation in HIV-infected patients is a key challenge for chronic kidney disease (CKD) diagnosis and drug dosing of antiretroviral agents. Serum creatinine is an imperfect marker of GFR, particularly in this population [1]. Nevertheless, the equation based on serum creatinine developed by the Chronic kidney disease-epidemiology collaboration (CKD-EPI) outperformed serum cystatin C-based equations in HIV-infected patients for CKD diagnosis [2,3]. Consequently, the recent guidelines of the Infectious diseases society of America (IDSA) for the management of CKD in HIV-infected patients recommend the use of CKD-EPI for CKD diagnosis [4]. However, Cockcroft and Gault (CG) formula is still recommended for antiretroviral (ARV) dosing [4]. Only one study has so far focused on GFR estimation for drug dosing in HIV-infected patients [5]. In an American cohort of HIV-infected patients conducted in the United States, CKD-EPI was associated with a higher concordance with measured GFR than CG and the Modification of died in renal diseases (MDRD) study equations, for assignment to the Food and Drug Administration (FDA) designated kidney function categories [5]. These results need to be confirmed in European HIV-infected patients, as patients are mostly Caucasians and as hepatitis B virus (HB V) and hepatitis C virus (HCV) co-infections are less frequent [5]. Moreover, the availability of new antiretrovirals (dolutegravir, rilpivirine) [6,7] or boosters (cobicistat) [8] interfering with tubular transporters of creatinine leads physicians to monitor more closely GFR in patients with normal kidney function to prevent renal adverse events. Consequently, we evaluated the concordance between the most frequently used GFR estimating equations (CG, MDRD, CKD-EPI) and a gold standard method for GFR measurement in our French cohort to improve decision making about prescription of ARVs in HIV-infected patients with normal estimated GFR (eGFR).

2. Patients and methods

2.1. Study population

Patients were recruited from the department of Infectious diseases of the university hospital of Saint-Étienne (France). Eligible patients were 18 years old, with confirmed HIV status.

Exclusion criteria were pregnancy, history of allergy, thyroid dysfunction, recent acute kidney injury, and treatment with metformin, steroids, trimethoprim, or cimetidine. The protocol was submitted and approved by Saint-Étienne's hospital institutional review board. The study was conducted in full compliance with the amended declaration of Helsinki following approval from the local ethical committee.

2.2. GFR measurement

GFR measurements were based on plasma clearance of iohexol (Omnipaque 300 GE Healthcare) as previously described [3]. GFR was calculated using a previously described protocol [9]. Measured GFR was indexed to Body surface area (BSA) as estimated by the Dubois & Dubois formula [10].

2.3. Laboratory methods

Blood and urine samples were stored at -80 °C. Serum creatinine was measured by isotope dilution mass spectrometry (IDMS)-traceable enzymatic method (Ortho Clinical diagnostics, United Kingdom, coefficient of variability [CV] 5.6% at 0.71 mg/dL, and 2.1% at 5.82 mg/dL). HIV viral load was determined by Abbott m2000 real-time HIV-1 assay (Abbott diagnostics, France). CD4+ lymphocyte count was measured by flow cytometry at the time of GFR measurement.

2.4. Analysis of the performance of GFR estimating equations and statistics

GFR was estimated with CG [11], MDRD [12], and CKD-EPI equations [13]. GFR was estimated using serum creatinine, on the day it was measured. As guidelines for drug dosing are not indexed to BSA, eGFR MDRD and CKD-EPI 2009 was not indexed to mL/min, multiplying eGFR by patient's BSA divided by 1.73 m^2. We did not use African-American (AA) coefficient factor for MDRD and CKD-EPI calculations, as a previous study demonstrated that it was not applicable to black subjects from Africa, Europe, or Antilles [14]. The percentages of participants assigned to each kidney function categories using two breakpoints (> 90 mL/min and > 70 mL/min) were calculated based on measured GFR and kidney function estimates from the five equations: CG, MDRD, CKD-EPI, and MDRD and CKD-EPI not indexed to BSA. Concordance and discordance for assignment to categories between measured GFR and each of the estimates were calculated. Significance of the differences in concordance for the assignment to kidney function categories was tested using McNemar's test. Each patient was included

in one of three categories (concordance between eGFR and mGFR, overestimation of GFR by eGFR, and underestimation of GFR by eGFR).

As in routine practice many physicians do not convert CKD-EPI and MDRD into mL/min for drug dosing, we also examined concordance rates between GFR, and MDRD and CKD-EPI adjusted to BSA. *P*<0.05 was considered statistically significant. Statistical analyses were performed using SAS software, version 9.1 (SAS institute, Cary, NC).

3. Results

A total of 230 HIV-infected patients were enrolled between February 2011 and December 2013. Mean age was 48±10 years, and 18% of patients were female. Mean body mass index was 24 ±4 kg/m^2 and 93% of patients were Caucasians (Table 1). Most patients received antiretrovirals and had undetectable HIV viral load at the time of GFR measurement (92% and 84% of the whole study population, respectively). Mean measured GFR was 95 ±23 mL/min/1.73 m^2 and 101 ±28 mL/min. One hundred and thirty-three (58 %) patients had mGFR > 90 mL/min, and 183 (79.5%) had mGFR > 70 mL/min.

Table 2 shows concordance rates and discordance rates (over-estimation and underestimation) between eGFR and mGFR to the assigned kidney function categories (> 90 mL/min and >70 mL/min). At the breakpoint of 90 mL/min, the use of MDRD for drug dosing was associated with a higher discordance rate of 35%; discordance rates for CKD-EPI and CG were similar and lower (27% and 27%) (*P* < 0.05 MDRD vs CKD-EPI and CG). Uses of non-indexed CKD-EPI and MDRD were more likely to result in assignment to a GFR > 90 mL/min, whereas use of CG was associated with a 14% risk to assign patients to GFR < 90 mL/min. Mean GFR of patients wrongly assigned to GFR > 90 mL/min was 79.5 (71-86) for CG, 77.5 (71-85) for non-indexed CKD-EPI, 77 (67-82) for non-indexed MDRD, 76.5 (71-82) for CKD-EPI, and 75 (67-81) for MDRD (*P* = NS). The proportion of patients wrongly assigned to the GFR category > 70 mL/min is 6, 7, 8, 9, and 9% (i.e., overestimation) for CG, non-indexed CKD-EPI, non-indexed MDRD, and CKD-EPI, and MDRD respectively (*P* = NS). Mean GFR of patients whose GFR was overestimated at GFR category < 70 mL/min was 64 mL/min (62-66) for CG, and 63 mL/min (56-66) for BSA-indexed and non-indexed MDRD, and for BSA-indexed and non-indexed CKD-EPI (57-66) (*P* = NS).

Table 1 : Participants' characteristics (n [%] for categorical variables, mean [±SD, min and max]

for continuous variables). *Caractéristiques des participants (n [%] pour les variables catégorielles et moyennes avec les écart-types, minimum, maximum pour les variables continues).*

Main characteristics of the population	***n* = 230**
Age (year) [range]	48 ± 10 [22-84]
Female	42(18%)
Time since HIV infection diagnosis (years)	13 ± 7 [0-29]
Weight (kg)	71 ± 13 [42-108]
Height (cm)	172 ± 8 [155-195]
African origin	16 (7%)
Body mass index (kg/m²)	24 ±4 [17-37]
<18	10 (4%)
<25	151 (65%)
25<BMI<30	55 (24%)
>30	24 (10%)
Diabetes	11 (5%)
Hypertension	39 (17%)
Smoker	90 (39%)
Intravenous drug user	13 (6%)
cART	212 (92%)
Tenofovir disoproxil fumarate use	131 (57%)
Ritonavir-boosted protease inhibitors	131 (57%)
Lopinavir	11 (5%)
Atazanavir	31 (13%)
Darunavir	89 (39%)
HIV viral load	
Undetectable (< 40 copies/mL)	194 (84%)
< 1000 copies/mL	16 (7%)
> 1000 copies/mL	21 (9%)
CD4 (cells/µL)	600 ± 275 [55-1840]
C-reactive protein (median, range)	3 (3-55)
Hepatitis B	11 (5%)
Hepatitis C	22 (10%)
ACR (mg/g) (n = 229)	40.8 ± 130.9 [1.5-1122.1]
<30	187 (82%)
30-300	36 (16%)
300-1000	3 (1%)
>1000	3 (1%)
Creatinine (mg/dL)	0.86 ±0.16 [0.51-1.48]
Iohexol GFR (ml/min/l.73 m²)	95 ± 23 [48-189]
Iohexol GFR (mL/min)	101 ± 26 [50-189]
Chronic kidney disease (CKD) stage (defined on iohexol)	
GFR > 90 mL/min/1.73 m²	133 (58%)
GFR 60-89 mL/min/1.73 m²	82 (36%)
GFR 45-59 mL/min/1.73 m²	15 (7%)
Hyperfiltrating status (GFR ≥ 120mL/min/1.73 m²)	27 (12%)
GFR categories for concordance measurement	
mGFR > 90 mL/min	133 (58%)
70 mL/min < mGFR < 90 mL/min	50 (22%)
mGFR < 70 mL/min	47 (20%)

cART: combined antiretroviral therapies; ACR: urine albumin/creatinine ratio; GFR: glomerular filtration rate; mGFR: measured GFR.

Table 2: Concordance between estimated GFR and measured GFR at two breakpoints (90 and 70mL/min) (183 patients [79.5%] had a GFR>70 mL/min, and 133 patients (58%) had a GFR > 90 mL/min). *Concordance entre le débit de filtration glomérulaire estimé et mesure à deux valeurs seuils (90 et 70 mL/min) (183 patients [79,5%] avec un DFG mesure supérieur à 70 mL/min et 133 patients [58 %] avec un DFG mesure superieur a 90 mL/min).*

Estimators	Breakpoint 70 mL/min			Breakpoint 90 mL/min		
	Concordance (%)	Overestimation (%)	Underestimation (%)	Concordance (%)	Overestimation (%)	Underestimation (%)
CG	208 (90)	13 (6)	9 (4)	168 (73)	30 (13)	32 (14)
Not-indexed to BSA CKD-EPI	207 (90)	17 (7)	6(3)	170 (74)	44 (19)	16 (7)
Not indexed to BSA MDRD	205 (89)	18 (8)	7 (3)	166 (72)	37 (16)	27 (12)
CKD-EPI	203 (88)	21 (9)	6 (3)	168 (73)	42 (18)	20 (9)
MDRD	199 (86)	21 (9)	10 (4)	150 (65)	37 (16)	43 (19)

BSA: body surface area; CG: Cockcroft and Gault; MDRD: modification of died in renal diseases.

4. Discussion

We had previously demonstrated that CKD-EPI was the most accurate equation for estimating GFR in European HIV-infected patients [3]. In this enlarged study population, we observed that concordance between mGFR and eGFR for the assignment to normal kidney function category (i.e. 90 mL/min) was similar for CG and CKD-EPI and poorer for MDRD. This observation may in part be explained by the mean GFR observed in our study population, which is greater than 90 mL/min/1.73 m^2, while MDRD was obtained from a population presenting with kidney disease with lower GFR [12]. Therefore, CKD-EPI more frequently overestimates GFR leading more often than CG to overexposure to antiretroviral agents. CG was already discussed as a conservative estimator to limit higher dosage prescription [15]. However, for the GFR < 90 mL/min category, the mean GFR of patients, with overestimated GFR by CKD-EPI and CG, was not different while the mean bias was greater for CG than CKD-EPI (data not shown). We performed an analysis using the standard reported units of mL/min/1.73 m^2, as physicians are not used to convert MDRD and CKD-EPI into mL/min for drug adjustment. Concordance rates of CKD-EPI were similar to non-indexed CKD-EPI in our population. The absence of difference between non-indexed and indexed CKD-EPI may be explained by only few patients with extreme BMI [16]. Our results support the use of CKD-EPI for drug dosing in HIV-infected patients. However, the use of IDMS-standardized creatinine measurement is required to use CKD-EPI. Physicians must check the technique used to measure creatinine before estimating GFR with CKD-EPI.

To the best of our knowledge, Okparavero et al. are the only ones to have evaluated GFR estimating equations for drug dosing in HIV-infected patients in a cohort of 200 American HIV-positive patients [5]. CKD-EPI exhibited the highest concordance with measured GFR for assignment to FDA-designated GFR categories (> 80, 50-80, 30-50, < 30 mL/min). As in our study, MDRD exhibited lower concordance with mGFR than CKD-EPI and CG [5]. Consequently, MDRD should be avoided for estimating GFR in HIV-infected patients. In contrast with our results, in their drug simulation study, use of CG was associated with a higher risk of overexposure to teno-fovir than non-indexed CKD-EPI [5]. Cohorts' characteristics were quite different (52% of African-American in Okparavero's study; mean BMI 27 kg/m^2 vs 24 kg/m^2 in ours; more intravenous drug users in the American Cohort, higher proportion of patients with undetected viral load in ours). We did not use the same GFR categories. We chose 90 mL/min, and 70 mL/min as breakpoints for the following reasons: 90 mL/min is the knot value to diagnose decreased GFR, and 70 mL/min is the threshold for renal interventions in the data collection on adverse events of anti-HIV drugs (D:A:D) study [17]. Seventy millilitre per minute is also the threshold for non-prescription of co-formulated elvitegravir/cobicistat/tenofovir/emtricitabine [4].

Our observation confirmed the difficulty to evaluate kidney function in HIV-infected patients. This situation is confusing for physicians. Several hypotheses can be drawn to explain suchvdifficulties. First, the use of BSA-indexed GFR estimates for drug dosing is controversial; it is nevertheless recommended to choose the most accurate method to estimate GFR for drug dosing [18]. Secondly, HIV-specific factors may influence endogenous markers of GFR such as serum creatinine [19]. In the near future, the increasing use of ARVs or boosters (cobicistat, dolutegravir, rilpivirine) interfering with creatinine transporters (OCT2 for dolutegravir and rilpivirine, MATE1 for cobicistat) in renal tubule, will accentuate the difficulties for a reliable GFR estimation in HIV-infected patients [6,8,20]. In patients

receiving these new ARVs, cystatin C may be an imperfect alternative to serum creatinine for evaluating kidney function [1].

A discordant estimation of GFR could have major consequences resulting in inappropriate antiretroviral regimen as shown with underexposure [5] or overexposure in our drug simulation study. Overexposure may result in higher plasma concentrations of antiretroviral agents such as tenofovir, associated with an increased risk of renal impairment [21,22]. Moreover, underexposure to antiretrovirals in patients presenting with CKD may result in an excessive mortality [23].

Some limitations to our study must be considered. The study population included few patients (n = 27) with mGFR< 70 mm/min/1.73 m^2. Results observed in the subgroup of low GFR must thus be considered with caution. Our patients were almost all Caucasians. For patients with marked renal impairment (< 10% of our study population), an additional and later measurement of plasma iohexol is usually recommended. As very few patients were not receiving combined antiretroviral therapy, and very few women were included in the study, our results cannot be extrapolated to all HIV-infected patients. Strengths of our study were the use of a gold standard method to measure GFR, and the serum creatinine measurement with IDMS-traceable method. Our cohort reflects HIV-infected patients, receiving efficient combined antiretroviral therapy in high-income countries from Europe.

CKD-EPI exhibited similar concordance rate as CG for drug dosing. The use of a unique estimate for drug dosing and CKD detection would facilitate clinical decision. CKD-EPI should thus be the preferred GFR estimate in HIV-infected patients. Physicians must, however, keep in mind that the estimation of renal function provided by the GFR estimating equations probably remains suboptimal for HIV-infected patients. This could justify a GFR measurement for drug dosing specifically in patients with extreme age and BMI (or at risk of low estimated GFR performance).

Contribution of authors

A.G.B., P.D., CM., and O.M. designed the study protocol. A.G.B., F.L., E.B.N., and O.M. wrote the article. C.F., A.G.B., and O.M. performed the statistical analysis. F.L., C.C., A.F., and C.G. included patients in the study and took care of patient management.

Disclosure of interest

The authors declare that they have no competing interest.

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